Presentation of a Model for Virus Therapy of Cancer Tumors Using the Modified Prey Predator Population Dynamics

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Abstract

Prey predator population dynamics has been frequently studied in literature to model many robust but contrastive biological populations. In this paper, based on prey predator population dynamics, a nonlinear model to predict the behavior of virus treatment of cancer cells is suggested. Based on the goals of virus curing and consideration of some practical issues, the suggested model has the capability to cover these following cases: both cancer cells and viruses vanish, one is eliminated by the other, or both survive in a robust periodically convergent manner or both become divergent.

Relative to the values of some parameters such as the virus intrinsic growth rate, carrying capacity, capturing rate, half saturation constant, maximal tumor cells growth rate, and tumor cells mortality rate, and the initial population values of both tumor cells and viruses, some examples are solved. These examples exhibit logical and feasible behavior for the system. They show under which conditions the virus therapy fails or succeeds; as well when the bifurcation occurs or when the trajectories converge to a limit cycle.

Keywords

Cancer Tumours; Virus Therapy; Limit Cycle; Bifurcation; Predator Prey Model

Introduction

Cancer is one of biggest causes of death, thus finding ways to beat cancer is really vital. Many researches can be found in literature concerning about the cancer treatment, tumor cell behaviors, clinical cares, etc; but because the main source of change from cells to tumor and defected ones is not clearly known, the treatment of cancer is almost based on the reduction of the destructive effects of cell behaviors. Virus therapy is an almost new method used for some types of cancer to destroy tumor cells by injecting killer viruses into the core of infected cells. Practically, this method is based on a trial and error process whereas a model is constructed to investigate the behaviors of tumor cells, which is really important to improve the researches in this area and to help the medicos to treat such diseases. By means of the model, the cell behaviors can be investigated and then the treatment process gets controlled.

In the past decades, some researchers have tried to utilize the virus therapy method to cancer treatment. However, due to the lack of molecular biology statements for the viruses, until 1990 these techniques didn't attract sufficient attention. Based on recent accomplishments in molecular biology of the viruses, the conventional methods in cancer treatment such as chemotherapy and radiotherapy can be replaced by virus therapy. The main superiority of the last method with respect to chemotherapy and radiotherapy is that the former kills the defected cells only see for example (Daniel Cervantes et. al. 2008)

Many mathematical models have been suggested for virus therapies of cancer tumor; see for example (Artem. S. et al. 2006, Dominik Wodarz, 2001. Zeljko Bajzer, et.al, 2008. Faina S, et al, 2007. Georgy P Karev, et al, 2006). With respect to their advantages, they cannot cover the whole dynamics of the process because in some of them, the death of all cancer cells cannot be reached or, for example, the coexistence of cancer cells and viruses is not probable. Although the reference (Dominik Wodarz. et al. 2009), presented an almost good model but all the probable coexistence cases of tumor cells and viruses

were not covered. In reference (Manju Agarwal et. al. 2011), a good coverage over the probable cases is also seen. SH Thorne and CH Contag (2008) studied the improvement of therapeutic benefits of cell-based delivery when the biological characteristics of oncolytic viruses and immune cells are integrated. Another approach studying the coexistence of two predators on one prey (see Irakli Loladze et. al. 2004) may be used to model the virus therapy of cancers with two types of viruses.

The Modified Prey Predator Model

Based on the famous prey predator model that was presented in (Bingtuan LI and Yang Kuang, 2007), a modified model is proposed in this article to predict the dynamics of the population of both viruses and tumor cells. Here the following equations are in use to describe the dynamics:

$$x'(t) = rx(1-\frac{x}{K}) - \frac{cxy}{x+my} \quad (1)$$

$$y'(t) = y(\frac{fx}{x+my} - d) \quad (2)$$

Where x and y are the population of prey (tumor cells) and predator (virus), respectively. In addition, r, k, c, m, f, and d , the positive constants demonstrate virus intrinsic growth rate, carrying capacity, capturing rate, half saturation constant, maximal tumor cells growth rate, and tumor cells mortality rate, respectively. For simplicity, using following non dimensional parameters,

$$x \to Kx, y \to Ky/m, t \to mt/c \quad (3)$$

one can reach such the following format:

$$x'(t) = \alpha x(1-x) - \frac{xy}{x+y} \quad (4)$$

$$y'(t) = -\beta y + \frac{\kappa xy}{x+y} \quad (5)$$

where:

$$\alpha = \frac{rm}{c}, \beta = \frac{dm}{c}, \kappa = \frac{fm}{c} \quad (6)$$

If both x and y take positive values, relations (4) and (5) are reduced to:

$$x'(t) = \alpha x(1-x)(x+y) - xy \quad (7)$$

$$y'(t) = -\beta y(x+y) + \kappa xy \quad (8)$$

Using a change of variable,

$$t \to t(x+y) \ , \quad (9)$$

and then Briot–Bouquet's transformation,

$$x \to x \ , \quad y \to yx \ , \ t \to t/x \ , \quad (10)$$

one can reach:

$$x'(t) = x[\alpha - \alpha x - (1-\alpha)y - \alpha xy] \quad (11)$$

$$y'(t) = y[(\kappa - \alpha - \beta) + \alpha x + (1-\alpha-\beta) + \alpha xy] \quad (12)$$

Replacing $x \to x/\alpha$ in (11) and (12), one can obtain:

$$x'(t) = x[\alpha - x - (1-\alpha)y - xy] \quad (13)$$

$$y'(t) = y[(\kappa - \alpha - \beta) + x + (1-\alpha-\beta) + xy] \quad (14)$$

α and $\nu = \kappa - \alpha - \beta$ (or equivalently α and κ) are utilized as our unfolding parameters while β is fixed. In (13 & 14) there are two second order terms whose coefficients depend on α. Then these terms are decomposed and rewritten (13 & 14) as:

$$x'(t) = x(\alpha - x - y) + x(\alpha y - xy) \quad (15)$$

$$y'(t) = y(\nu + x + (1-\beta)y) \quad (16)$$

Using the transformations

$$x \to \varepsilon x \ , \ y \to \varepsilon y \ , \ \alpha = \varepsilon \nu_1 \ ,$$

$$\nu = \frac{-2(1-\beta)}{2-\beta}\varepsilon\nu_1 + \nu_2\varepsilon^2 \quad (17)$$

and rescaling time $t \to t/\epsilon$, we convert (15 & 16) to:

$$x'(t) = x[\nu_1 - x - y] + \varepsilon(\nu_2 xy - x^2 y) \quad (18)$$

$$y'(t) = y[\frac{-2(1-\beta)}{2-\beta}\nu_1 + x + (1-\beta)] + \varepsilon(\nu_2 y - \nu_1 y^2 + y^2 x) \quad (19)$$

The system of equations (18 & 19) describes the nonlinear model of the viruses and cancer cell interaction in this work.

Examples

The parameters υ_1, υ_2, ϵ, and β in (18 & 19) related to r, k, c, m, f, and d have been introduced previously as virus intrinsic growth rate, carrying capacity, capturing rate,

half saturation constant, maximal tumor cells growth rate, and tumor cells mortality rate, respectively. Here, based on these parameters, the stationary points and the behavior of the system are obtained and drawn in phase plane.

Case I The Virus Therapy Fails

By means of the values presented in Table 1, and the solution to the equations, the behavior drawn in Fig. 1 is confronted.

TABLE 1 THE VALUES OF PARAMETERS USED IN CASE 1

ν_1	ν_2	β	ε
40	0.1	2.5	0.00001

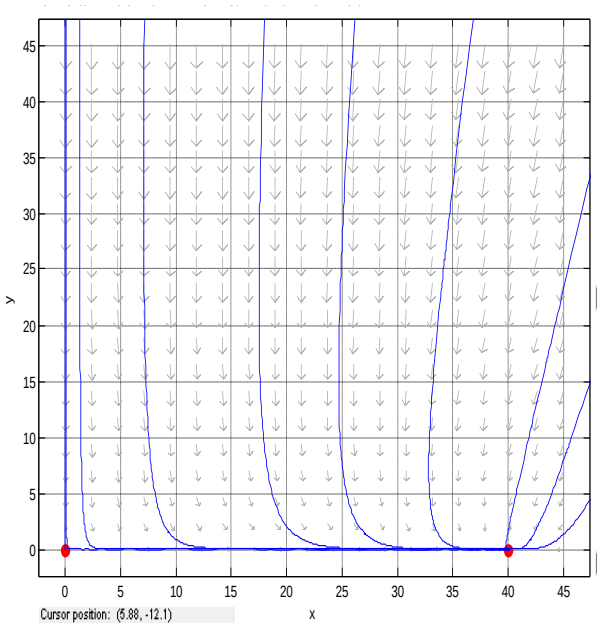

FIG. 1 THE BEHAVIOR OF THE SYSTEM IN PHASE PLANE FOR CASE I

(x: population of tumor cells; y: population of viruses)

According to this figure, only two saddle points constructed at (0, 0) and (40, 0) are the stationary points of the system. Fig. 1 shows also that the virus therapy in this case fails such that the trajectories initiated from each initial condition (all points in the phase plane except y axis) terminate to stationary point (40,0), meanings that after sufficient amount of time, the viruses are vanished by the tumor cells.

Case II The Virus Therapy Succeeds

By means of the values presented in Table 2, as well as the solution to the equations, the behavior drawn in Fig. 2 is confronted as well which shows a bifurcation. In other words, since the factor β (see (6) also) reduces to smaller values, the number of the stationary points and the whole behavior completely change.

TABLE 2 THE VALUES OF PARAMETERS USED IN CASE 2

ν_1	ν_2	β	ε
40	0.1	1.5	0.00001

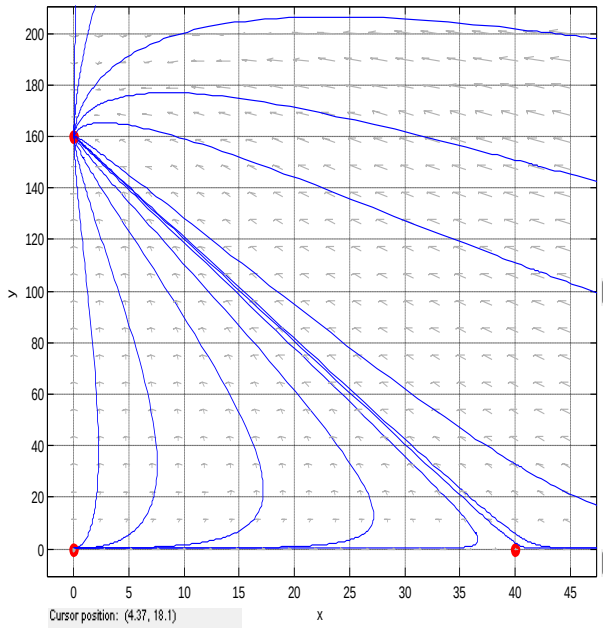

FIG. 2 THE BEHAVIOR OF THE SYSTEM IN PHASE PLANE FOR CASE II

(x: population of tumor cells; y: population of viruses)

Based on this figure, a source at (0, 0), a saddle point at (40, 0) and a sink at (0,159.8721) can be seen, as well as shows that the virus therapy in this case succeeds such that the trajectories initiated from each initial condition (all points in the phase plane except ones on the convergent manifold of the saddle point) terminate to stationary point (0,159.8721), meaning that after sufficient amount of time, the tumor cells are vanished by viruses.

Case III Coexistence of Both Viruses and Tumor Cells

By means of the values presented in Table 3, and the solution to the equations, the behavior drawn in Fig. 3 is confronted as well which shows another bifurcation also the famous robust limit cycle usually seen in prey predator models. In other words, since the factor β (see (6) also) reduces to smaller values but υ_2 becomes larger,

the number of the stationary points and the whole behavior of system completely change.

TABLE 3 THE VALUES OF PARAMETERS USED IN CASE 3

ν_1	ν_2	β	ε
40	0.4	0.6	0.0005

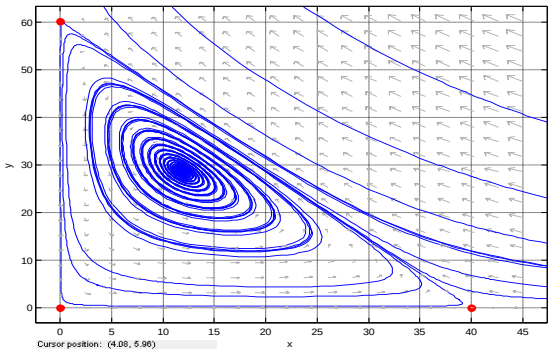

FIG. 3 THE BEHAVIOR OF THE SYSTEM IN PHASE PLANE FOR CASE III

(x: population of tumor cells; y: population of viruses)

Based on this figure, three saddle points at (0, 0), (40,0) and (0,60) and a stable focus at (12.062, 28.4) can be seen.

Fig. 3 shows also that the virus therapy in this case results in the coexistence between the viruses and the tumor cells. In this case the trajectories initiated from a point lain in the triangle constructed by three saddle points converge to the stable focus that presents a chronic illness. For other initial conditions, the tumor cells are reduced slowly but not completely removed.

Quantitatively, changing the parameters does not lead to significant changes in behavior, whereas the rate of response, stationary points, areas of attraction and region of the robustness of limit cycle will change. In Fig. 4, a slower dynamics and in Fig.5 the evolution of the limit cycle for the case 3 are drawn

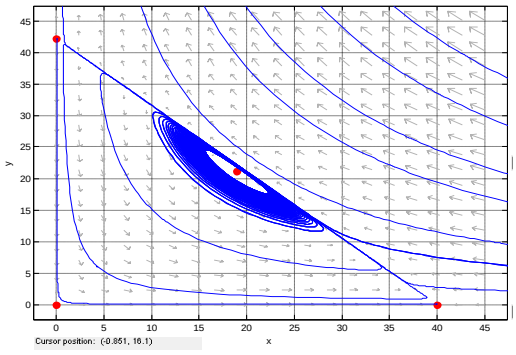

FIG. 4 THE BEHAVIOR OF THE SYSTEM IN PHASE PLANE SIMILAR TO CASE III BUT WITH SMALLER β AND LARGER υ_2

(x: population of tumor cells; y: population of viruses)

It is noted that the area constructed in the triangle in Fig. 4 is in direct relation to the squared value of υ_2. This may be utilized in validation of the model with experimental studies and prediction on the behavior for some standard practical cases.

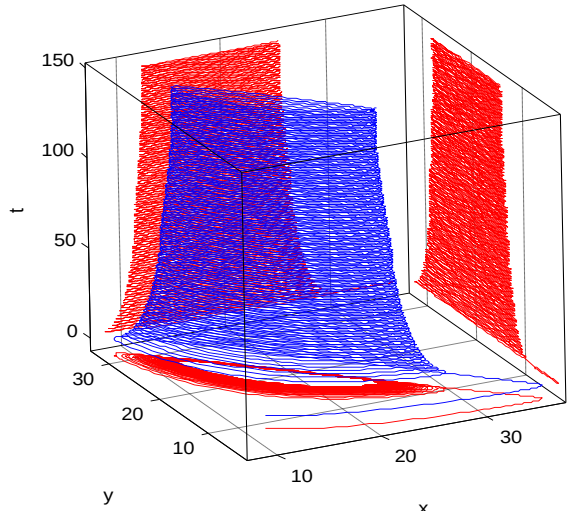

FIG. 5 THE EVOLUTION OF THE LIMIT CYCLE OF FIG. 4

(x: population of tumor cells; y: population of viruses)

Local Stability Analysis of Equilibrium Points

Local stability analysis is concerned with the stability of a nonlinear system near its equilibrium points. It is a formalization of the intuition that a nonlinear system should behave similarly to its linearized approximation for small range motions. See (Jean-Jacques E. Slotine and Weiping LI. 2001, Erwin Kreyszig, 2010) for more details.

Here for our model, to check the stability near equilibrium points, the variational matrix is constructed by differentiating the right hand side of Equations (18&19) with respect to , x and y. The entries of the general variational matrix V for point P become:

$$V(p)=\begin{bmatrix} A & B \\ C & D \end{bmatrix} \tag{20}$$

Where

$$A=\nu_1-2x-(\varepsilon\nu_1-2\varepsilon x-1)y \tag{21}$$

$$B=\varepsilon\nu_1 x-\varepsilon x^2-x \tag{22}$$

$$C=y+\varepsilon y \tag{23}$$

$$D = \frac{-2(1-\beta)}{2-\beta} v_1 + x + 2(1-\beta)y + \varepsilon v_2 - 2\varepsilon v_1 y + 2\varepsilon xy \quad (24)$$

Now for studied cases, the local stabilities in equilibrium points are investigated. To explore the local stability of trivial equilibrium points, the eigenvalues of V (P) at stationary points are computed and analyzed.

Case I

1) Local Stability Analysis of P(0,0)

The V (P) and its eigenvalues are:

$$V(p(0,0)) = \begin{bmatrix} 40 & 0 \\ 0 & -240 \end{bmatrix}$$

$$\lambda = 40 \ , \ \lambda = -240$$

So we have a saddle point at P (0, 0)

2) Local Stability Analysis of P(40,0)

The V (P) and its eigenvalues are:

$$V(p(40,0)) = \begin{bmatrix} -40 & -40 \\ 0 & -200 \end{bmatrix}$$

$$\lambda = -40 \quad , \quad \lambda = -200$$

So we have a nodal sink point at P (40, 0)

Case II

1) Local Stability Analysis of P(0,0)

The V (P) and its eigenvalues are:

$$V(p(0,0)) = \begin{bmatrix} 40 & 0 \\ 0 & 80 \end{bmatrix}$$

$$\lambda = 40 \quad , \quad \lambda = 80$$

So we have a nodal source point at P (0, 0)

2) Local Stability Analysis of P(0,159.8721)

The V (P) and its eigenvalues are:

$$V(p(0,159.8721)) = \begin{bmatrix} -119.8082 & -9.9057e-7 \\ 160.1277 & -80 \end{bmatrix}$$

$$\lambda = -119.8082 \quad , \quad \lambda = -80$$

So we have a nodal sink point at P (0,159.8721)

3) Local Stability Analysis of P(40,0)

The V (P) and its eigenvalues are:

$$V(p(40,0)) = \begin{bmatrix} -40 & -40 \\ -5.0741e-7 & 120 \end{bmatrix}$$

$$\lambda = -40 \quad , \quad \lambda = 120$$

So we have a saddle point at P (40,0)

Case III

1) Local Stability Analysis of P(0,0)

The Eigenvalues of V (P) at point P(0,0) is given by:

$$V(p(0,0)) = \begin{bmatrix} 40 & 0 \\ 0 & -22.8589 \end{bmatrix}$$

$$\lambda = 40 \quad , \quad \lambda = -22.8589$$

So we have a saddle point at P (0, 0)

2) Local Stability Analysis of P(11.8307,28.5718)

The V (P) and its eigenvalues are:

$$V(p(11.8307,28.5718)) = \begin{bmatrix} -11.9997 & -11.664 \\ 28.9799 & 11.0263 \end{bmatrix}$$

$$\lambda = -0.486697 \pm 14.3344i$$

So we have a spiral sink or stable focus at this point.

3) Local Stability Analysis of P(0,60.1498)

The V (P) and its eigenvalues are:

$$V(p(0,60.1498)) = \begin{bmatrix} -18.9462 & 0 \\ 61.9589 & 22.8569 \end{bmatrix}$$

$$\lambda = -18.9462 \quad , \quad \lambda = 22.8569$$

So we have a saddle point at P (0, 60.1498).

4) Local Stability Analysis of P(40,0)

The V (P) and its eigenvalues are:

$$V(p(40,0)) = \begin{bmatrix} -40 & 40 \\ -3.5752e-7 & 17.1431 \end{bmatrix}$$

$$\lambda = -40 \quad , \quad \lambda = 17.1431$$

So we have a saddle point at P (40, 0).

Conclusion

In this paper, a modified model based on the prey predator population dynamics is presented with the capability to predict and investigate the practical clinical cases. Relative values of some parameters to the virus

intrinsic growth rate, carrying capacity, capturing rate, half saturation constant, maximal tumor cells growth rate, and tumor cells mortality rate, and the initial population values of both tumor cells and viruses, some examples are solved which exhibit logical and feasible behavior for the system. They show under which conditions the virus therapy fails or succeeds; also when the bifurcation occurs or when the trajectories converge to a limit cycle.

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